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<b>(54) Title:</b> A COMPOSITION FOR THE TREATMENT OF ANDROGENETIC ALOPECIA AND HIRSUTISM  <b>(57) Abstract</b>  A pharmaceutical or cosmetic composition is provided for the prevention and/or treatment of androgenic alopecia and/or hirsutism which comprises a lipophilic extract of fruits of <i>Serenoa repens</i> (SR) plants, fractionation products of said extract, and purified active substances obtained from said extract and optionally comprising one or more additional active ingredients.		

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## A COMPOSITION FOR THE TREATMENT of ANDROGENETIC ALOPECIA AND HIRSUTISM

### FIELD OF THE INVENTION

The present invention concerns a composition for the prevention or treatment of androgenetic alopecia or hirsutism.

### 5 BACKGROUND OF THE INVENTION

Androgenetic alopecia, widely referred to as "*male-pattern alopecia*", actually refers to common baldness which is a very prevalent phenomena in men and also occasionally in women. Androgenic alopecia is a physiological process occurring in genetically predisposed individuals during  
10 which terminal hair follicles are progressively transformed into villous hair follicles and the reduction in the size of the affected follicles, results in a reduction in the diameter of the hairs they produce and subsequent hair loss occurs (Rook/Wilkinson/Ebling - Textbook of Dermatology, Eds. - Champin, R.H., Buton, J.L., Ebling, F.J.G., Vol. 4, 5th edition, Blackwell Scientific  
15 Publications, Oxford, Chapter 63:2571-2577).

Androgenic alopecia has been shown to depend on androgens and the active androgen in the balding scalp appears to be dihydrotestosterone (DHT). DHT is produced from testosterone through the action of the 5 $\alpha$ -reductase enzyme. A correlation between the level of the 5 $\alpha$ -reductase  
20 enzyme in the scalp and baldness has been shown: elevated 5 $\alpha$ -reductase levels have been detected in the frontal scalp of balding men (Bingham, K.D. *et al.*, *J. Endocrinol.*, 57:111-121 (1973)) and human males having 5 $\alpha$ -reductase deficiency syndrome did not develop hair loss (Ebling, F.J.G., *Clin. Endocrinol. Metab.*, 319-339, (1986)).

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In view of the fact that hair loss is a wide spread phenomena which may begin at any age after puberty and may at times become apparent as early as the age of 17 in the normal male and the age of 25-30 in the endocrinologically normal female, there is an ongoing search for suitable treatments to prevent baldness in male or female humans.

In males suffering from alopecia, anti-androgens are unsuitable for use in the treatment of baldness in view of their many side-effects including feminization and a compromise in the individual's sexual function. In some cases, anti-androgens may be used for the treatment of baldness in women but, such drugs have been shown only to prevent further progression of baldness and not to induce regrowth of hair follicles.

Inhibitors of the  $5\alpha$ -reductase enzyme cause a reduction in the level of DHT both in the prostate as well as in the skin. Such  $5\alpha$ -reductase inhibitors do not block the binding of testosterone to its receptors and therefore have not been reported to cause side effects or sexual problems in human males receiving treatments comprising such inhibitors (Metcalf, B.W., *et al.*, *Trends Pharmacol. Sci.*, **10**:491-495, (1989)). There are two forms of  $5\alpha$ -reductase enzymes: type 1 present in all skin tissue and predominating the scalp of adult men and type 2 located mainly in genital skin.

One treatment that has been shown to enhance regrowth of terminal hair in humans is the drug Minoxidil (Uno H., *et al.*, *J. Am. Acad. Dermatol.*, **16**:657-668, (1987)). Minoxidil is a piperidinopyrimidine derivative and a potent vasodilator which is effective when administered orally for the treatment of severe hypertension. Recently, it was shown that Minoxidil is a weak inhibitor of the enzyme  $5\alpha$ -reductase type 1 (Mellin, T.N., *J. Steroid Biochem. Molec. Biol.*, **44**:121-131, (1993)). However, even when applied topically, Minoxidil was shown to convert villous to terminal hair at the margins of the scalp in only about 30% of treated individuals and complete covering of the bald area of treated individuals was accomplished in

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less than 10% of such responding individuals. Another 5 $\alpha$ -reductase inhibitor, Finasteride, when administered orally, was shown to increase hair weight in stumptail macaque monkeys which have been used as a model for androgen-dependent human alopecia (Diani, A.R., *et al.*, *J. Clin. Endocrinology and Metabolism*, 74:345-350, (1992)).

Extracts obtained from the fruit of *Serenoa repens* (SR) plants have been reported to possess anti-androgenic activity (Sultan, C., Terraza, A, *J. Steroid Biochem.*, 20:515-519, (1984)). Recently, it has been shown that such SR extracts have a non-competitive inhibitory activity of the enzyme 5 $\alpha$ -reductase (type 1) (Delos, S., Iehle, C., *J. Steroid Biochem. Molec. Biol.*, 48:347-352, (1994)). SR extracts have been used for many years for the treatment of benign prostatic hypertrophy (BPH) in humans (Briley, M. *et al.*, *Br. J. Pharmacol.*, 79:327 (1983)). An example of such a drug comprised of an SR extract and used for the treatment of BPH in humans is the drug Urgenin<sup>™</sup> (produced by Medhouse, Germany and known also by the name Prostaserene<sup>™</sup>). The SR extracts used for the treatment of BPH in humans had no effect on the human plasma levels of testosterone, follicle-stimulating hormone and LH (Casarosa, G. *et al.*, *Clin. Therap.*, 10:585 (1988)) and showed very few side effects in very low percents of treated BPH patients (Champault *et al.*, *Br. J. Clin. Pharmacol.*, 18:461, (1984)).

The basic SR extract is a mixture of free fatty acid and sterol components and processes for the preparation of such extracts of SR fruits have been previously disclosed (see for example FR-A-2480754). Recently new processes for obtaining SR extracts which have a significantly higher anti-androgenic activity as compared to total lipophilic extracts of SR have also been disclosed (see for example WO 88/07866 and EPO 492305).

In addition to the treatment of BPH, dermatological compositions comprising a lipid fraction obtained from SR fruits has also been described as suitable for the treatment of acne (EPA 204877). The SR

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extracts were shown to be efficient in the treatment of disorders of sebaceous and pilosebaceous glands and no irritation of the treated skin was reported by the treated individuals. However, recent findings have indicated that the development of acne is actually effected by the levels of testosterone in the individual rather than on the level of DHT (Thiboutot, D.M. *et al.*, *J. Invest. Dermatol.*, 98:581 (1992)).

## GENERAL DESCRIPTION OF THE INVENTION

In accordance with the present invention lipophilic extracts from fruits of *Serenoa repens* (SR) plants are used for the treatment of androgenic dependent common baldness in humans. In addition, in accordance with the present invention, such lipophilic extracts may also be used for the treatment of hirsutism (overgrowth of hair). It is known that overgrowth of hair on parts of the body other than the scalp, e.g. moustache (mainly in women), arms, breasts, etc., is androgen dependent. However, while high levels of DHT in the scalp cause loss of scalp hair leading eventually to baldness, high levels of this hormone in other body parts has an opposite effect, i.e. bringing to hair overgrowth. These two phenomena are indeed intertwined in many individuals (e.g. males which are bald but have an overgrowth of hair on other body parts). Accordingly, lipophilic extracts of SR fruit are also used in accordance with the present invention to treat hirsutism.

In addition to lipophilic extracts of SR fruit, also useful in accordance with the present invention are various fractionation products of such extracts, e.g. filtration products (using the filtrate or the retentate, depending on the type of filter which is used), products which result from chromatography fractionation, e.g. by high pressure liquid chromatography (HPLC) or thin layer chromatography (TLC), products obtained by further extraction of the lipophilic extracts using a variety of organic solvents, etc. In

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addition, also useful in accordance with the invention is a purified active substance obtained from lipophilic extracts of SR fruits as well as such a product obtained by synthesis or bioprocessing.

The lipophilic extract obtained from SR fruits, an active  
5 fractionation product thereof, or the purified active substance of such an extract, will be referred to herein collectively at times as "*active agent*".

The present invention provides by a first of its aspects, a pharmaceutical or cosmetic composition for the prevention or treatment of androgenic alopecia, comprising, as an active ingredient, an effective amount  
10 of said active agent. At times, said active agent, particularly where said active agent is said lipophilic extract, may be included as such in the composition. Occasionally, however, said composition may also comprise a pharmaceutically or cosmetically acceptable carrier.

In accordance with another aspect of the invention there is  
15 provided a method for the treatment of androgenic alopecia comprising administering to an individual in need an effective amount of said active agent.

In accordance with a further aspect of the invention there is provided use of said active agent for the preparation of a pharmaceutical or  
20 cosmetic composition for the treatment of androgenic alopecia.

By an additional aspect of the invention there is provided a pharmaceutical or cosmetic composition for the prevention or treatment of hirsutism, comprising, as an active ingredient, an effective amount of said active agent, optionally with a pharmaceutically or cosmetically assessable  
25 carrier.

The invention further provides a method of treatment of hirsutism comprising administering to an individual in need an effective amount of said active agent.

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By a still further aspect of the invention there is provided use of said active agent for the preparation of a pharmaceutical composition for the treatment of hirsutism.

The use of said active agent for the purpose of treatment or  
5 prevention of alopecia, in accordance with the invention, will be referred to herein at times as the "*anti-alopecia treatment*"; use of said active agent for the prevention or treatment of hirsutism, in accordance with the invention, will be referred to herein at times as the "*anti-hirsutism treatment*".

The term "*androgenetic alopecia*" refers to common baldness  
10 both in males and females which is dependent on androgens. As explained above, the main enzyme, the level of which is correlated with the extent of baldness in an individual, is the 5 $\alpha$ -reductase enzyme type 1, which is involved in the transformation of testosterone to dihydrotestosterone (DHT).

The term "*effective amount*" should be understood as meaning an  
15 amount of said active agent required to achieve a therapeutic effect. The effective amount required to achieve a therapeutic end result may depend on a number of factors including, for example, the age of the treated individual, genetic disposition, at what stage of baldness the treatment is administered, if the individual is a male or female, etc. The effective amount may also be  
20 dependent at times on the mode of administration, the site where said active ingredient is administered, etc. For example, where the therapeutic regime involves daily administration the effective amount of said active ingredient in each administration may be different than the effective amount in the case of a different therapeutic regime, e.g. several times per day or once every few  
25 days.

In anti-alopecia treatment in accordance with the invention, an effective amount of said active agent will be such an amount which will at least decrease the rate of hair loss or at times even prevent further loss of hair or induce hair regeneration. Namely, an effective amount of said active agent



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given within the framework of the anti-alopecia treatment of the invention will inhibit or delay progress of baldness. An effective amount of said active agent given within the framework of the anti-hirsutism treatment of the invention is an amount such which will inhibit further growth of unwanted  
5 hair or at times even cause loss of such hair.

The lipid extract of the SR fruit may be obtained by any of the known extraction processes including those described above. Thus, for example, the extract may be a total lipophilic extract having a ponderal yield of 10% starting from the vegetable material. Typically, such an extract is  
10 composed of about 85% fatty acids and about 15% by a mixture of ethyl and methyl esters of said acids, long-chained saturated and unsaturated alcohols in free and sterile form with the above acids and with sterols and triterpenic alcohols present in free and sterile form. In addition, the SR extract used in accordance with the invention may also be a lipophilic fraction which was  
15 further purified by known methods to improve its androgenic activity, e.g. by obtaining the alcoholic fraction of the total lipophilic extract having alkaline hydrolysis and extraction with water immiscible solvents (WO 88/07866) or by obtaining extracts having a high content of stable esters (EPA 0492305).

Said active agent may be administered, within the framework of  
20 the anti-alopecia treatment, at various stages of baldness in individuals. In accordance with one embodiment of the anti-alopecia treatment, said active agent is given to an individual for prevention of alopecia. For this purpose, individuals having a high probability of developing acute baldness may be treated with said active agent prior to the appearance of baldness in the  
25 individual or at very first stages of the development of baldness. The term "*prevention*", should be understood to mean either the prevention of baldness before its appearance or, alternatively, the prevention of the progression of the balding process from its first stages (slight loss of hair) to its more advanced stages (massive loss of hair to complete baldness). By another embodiment of

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the anti-alopecia treatment, said active agent is given to an individual for treatment of anti-alopecia. In accordance with this embodiment, the administration is intended to cause stimulation and regrowth of hair in bald areas.

5           The composition of the invention may be prepared in a variety of forms in which it may be applied to the treated individual. For example, the composition may be prepared and applied as a cream, a foam, a gel, a liposome emulsion etc. In addition, the pharmaceutical compositions, especially when administered routinely such as, for example, in the case of  
10 prevention, may be included within a shampoo or hair conditioner used regularly by the individual. In addition to said active agent, the composition of the invention may also comprise various additional inert materials such as inorganic minerals, ajuvents, stabilizing agents, surfactants, emulsifiers or dispersants. In addition, the composition may also contain other active  
15 ingredients such as, for example, zinc salts. The composition of the invention is typically applied to the treated individual topically by spreading it in the form of a cream solution or gel on the surface of the head skin to be treated. However, at times, it may be preferred to apply the composition of the invention also by other routes of administration such as, for example, by oral  
20 administration (per os) or parenteral, e.g. subcutaneous injection of the compositions. All components of the composition should preferably be non-toxic. In the case of a topical composition, the inclusion of ingredients which may have a small irritating effect may, at times, be tolerated.

Where said active agent is the lipophilic SR fruit extract, the  
25 amount thereof to be administered to the individual is typically about 100 mg to about 500 mg, preferably about 200 mg to about 400 mg, and desirably about 300 mg per day. As will be appreciated by the artisan, this amount may vary in accordance with various characteristics of the treated individual such as his or her weight, age, severity of the individual's baldness, whether the

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individual is receiving other treatments simultaneously with the compositions of the invention, etc. In addition, the mode of administration of the composition (topically, orally, etc.) will also effect the amount of the active agent to be administered.

5           The total daily active agent dose may either be administered in a single dose, may be dosed for several daily administrations or several daily doses may be combined for administration once every several days. The period of time in which the individual will be treated with the active agent of the invention will also vary depending on the specific situation. Thus, at  
10 times, the active agent may be administered continuously for a period of time; alternatively, the active agent may be administered over a first period of time, followed by a second period of time in which the individual is not treated and then resuming the treatment again for an additional third period of time; etc.

          The composition of the invention may at times be administered  
15 to an individual in combination with one or more additional treatments such as for example, in combination with a 5 $\alpha$ -reductase inhibitor such as minoxidil. The two or more treatments may then be administered to the person in need simultaneously or at alternative administration times.

          The invention will now be illustrated by the following  
20 non-limiting examples.

## EXAMPLES

### Example 1:     Formulations

          The following are some non-limiting examples of formulations  
25 of the compositions which may be used in accordance with the invention:

Cream:

An active fraction obtained from SR fruit - 60% by weight is dissolved in a carrier consisting, by volume, polyethylene glycol (PEG) (50%), conservative or absolute ethanol (30%) and water (20%).

5 Lotion:

SR fruit extract - 10% by weight, zinc sulphate 1% by weight and vitamin A 2% by weight are dissolved in a carrier consisting by volume of a conservative (30%), perfume (5%) and water (55%).

10 **Example 2: Testing potential SR formulations in Stumptail Macacue Monkeys**

The pathogenesis of baldness in the stumptail macacue monkeys and in humans appears to be similar and the stumptail macacue  
15 monkeys have been previously used as androgen-dependent models of human alopecia (Diani *et al.*, *supra*).

For testing potential formulations comprising the SR active agent of the invention, adult male balding stumptail macacue (*Macaca speciosa*) monkeys (body weight between 10-14 kg.) are used. The scalps of  
20 the monkeys all display frontal balding, showing sparse terminal hair and a predominance of vellous hair. The monkeys are maintained as described in Diani *et al.*, *supra*.

The hair growth of each monkey before, between and during the study is measured at 4-week intervals by shaving and weighing the hair  
25 from the defined one-inch square area (premarked before at the beginning of the test by methods known *per se*) in the center of the balding scalp. The hair collection is also performed by sedating each monkey as previously described (Diani *et al.*, *supra*).

The monkeys are divided into the following 4 groups, each  
30 group comprising 5 monkeys:

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The monkeys in Group 1 receive a topical administration of a cream (lotion or gel) comprising 60% by weight of the S.R. active agent and a carrier (e.g. the formulations of Example 1 above) once a day on the center of the bald area of the scalp using a paint brush.

5           The monkeys in Group 2 (control) receive a topical administration of the cream (lotion or gel) administered to the monkeys of Group 1 comprising the carrier only in the same manner as the monkeys in Group 1.

10           The monkeys in Group 3 receive a topical administration of the cream (lotion or gel) comprising 30% by weight of the S.R. active agent and a carrier twice a day (morning and evening) on the center of the bald area.

15           The monkeys in Group 4 (control) receive a topical administration of the cream (lotion or gel) that the monkeys in Group 3 receive comprising the carrier only twice daily at the same times during the day and in the same manner on the center of the bald area of the scalp.

          The measurement of the scalp hair weight ( $\text{mg}/\text{inch}^2$ ) are obtained and expressed as the change in weight compared to the scalp hair weight data of the monkey before the beginning of the treatment. The body weight (in kg) of each monkey is also measured at each hair collection.

20

#### Statistics:

          The obtained data is expressed as the mean scalp hair weight of the monkeys in a treatment group  $\pm$  SD. The sum of the four week changes in hair weight from the baseline measurement at the beginning of the experiment is subjected to analysis of variance and the differences among the treatment groups and the control groups are determined by using the non parametric Wilcoxon Rank Sum Test for unpaired data. Changes are considered statistically significant at a  $p < 0.05$ .

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The composition comprising the SR extract which will cause the greatest reduction in baldness in the scalp area of the monkeys will be used for testing as a treatment for alopecia in humans.

5   **Example 3: Treatment of human alopecia**

A group of 20 human males suffering from common male baldness are divided into two groups:

Individuals in Group 1 each receive daily topical administration of a cream or lotion comprising the SR active agent in accordance with the invention (either in a single dose or in a double dose and in a total amount  
10 according to the results of preliminary experiments in monkeys - see Example 2).

Individuals in Group 2 (control) each receive the same number of topical administrations of a composition comprising the carrier alone.

15   The bald area in the scalps of the treated males is determined at the beginning of the experiment and is measured every four weeks for 20 weeks.

At the end of the 20 week experiment, the effect of the compositions of the invention on reducing the size of the bald area in the scalp  
20 of the treated males is determined using the same statistical analysis described in Example 2 above.

**Example 4: Combined treatment of human alopecia**

Human males suffering from common male baldness are  
25 divided into five groups:

Group 1 receiving treatment similar to the treatment of Group 1 in Example 3 above;

Group 2 receiving a combined treatment consisting of daily topical administrations of a cream or lotion comprising a combination of the SR

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active agent in accordance with the invention as in Group 1 and 2% minoxidil;

Group 3 in which individuals receive topical administration of the composition of the invention and, on alternative days administration of a composition comprising 2% minoxidil in alcohol and propylene glycol;

Group 4 (control A) in which each individual receives the same number of topical administrations of a composition comprising the carrier of the composition of the invention alone; and

Group 5 (control B) wherein each individual receives a topical administration of a composition comprising the carrier of the composition of the invention (on days where individuals of Group 3 receive administration of this composition) and on alternative days receive a composition comprising the carrier of the composition comprising minoxidil (on days where individuals of Group 3 receive the minoxidil composition).

The effect of each treatment is analyzed as described in Example 3 above.

**CLAIMS:**

1. A pharmaceutical or cosmetic composition for the prevention or treatment of androgenic alopecia, comprising, as an active ingredient, an effective amount of an active agent selected from the group consisting of a lipophilic extract of fruits of *Serenoa repens* (SR) plants, fractionation products of said extract, and purified active substances obtained from said extract and optionally comprising one or more additional active ingredients for the prevention or treatment of androgenic alopecia.
- 5 2. A pharmaceutical or cosmetic composition according to Claim 1, wherein said additional active ingredient is minoxidil.
3. A pharmaceutical or cosmetic composition according to Claim 1 or 2 suitable for oral administration.
4. A method for the prevention or treatment of androgenic alopecia comprising administering to an individual in need an effective amount of an active agent selected from the group consisting of a lipophilic extract of fruits of *Serenoa repens* (SR) plants, fractionation products of said extract, and purified active substances obtained from said extract optionally in combination with an effective amount of one or more active agents for the prevention or treatment of androgenic alopecia.
- 15 5. A method according to Claim 4, wherein said active agent is administered to an individual in combination with an effective amount of minoxidil.
6. A method according to Claims 4 or 5, wherein said active agents are administered to an individual orally.
- 25 7. Use of an active agent selected from the group consisting of a lipophilic extract of fruits of *Serenoa repens* (SR) plants, fractionation products of said extract, and purified active substances obtained from said extract for the preparation of a pharmaceutical or cosmetic composition for



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the treatment of androgenic alopecia optionally adapted for use in combination with one or more additional active agents.

8. Use of an active agent according to Claim 7, wherein said additional active agent is minoxidil.

5 9. A pharmaceutical or cosmetic composition for the prevention or treatment of hirsutism, comprising, as an active ingredient, an effective amount of an active agent selected from the group consisting of a lipophilic extract of fruits of *Serenoa repens* (SR) plants, fractionation products of said extract, and purified active substances obtained from said extract and  
10 optionally comprising one or more additional active ingredients for the prevention or treatment of hirsutism.

10. A pharmaceutical or cosmetic composition according to Claim 9, wherein said additional active ingredient is minoxidil.

11. A pharmaceutical composition according to Claims 9 or 10,  
15 suitable for oral administration.

12. A method of treatment of hirsutism comprising administering to an individual in need an effective amount of an active agent selected from the group consisting of a lipophilic extract of fruits of *Serenoa repens* (SR) plants, fractionation products of said extract, and purified active substances obtained  
20 from said extract optionally in combination with an effective amount of one or more active agents for the prevention or treatment of hirsutism.

13. A method according to Claim 12, wherein said additional active agent is minoxidil.

14. Use of an active agent selected from the group consisting of a  
25 lipophilic extract of fruits of *Serenoa repens* (SR) plants, fractionation products of said extract, and purified active substances obtained from said extract for the preparation of a pharmaceutical composition for the treatment of hirsutism optionally adapted for use in combination with one or more additional active substances.

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15. A kit comprising a packaged first pharmaceutical or cosmetic composition in accordance with Claim 1 optionally together with a packaged second composition comprising minoxidil together with means for administration of said compositions and instructions for use thereof.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IL 98/00044

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A61K7/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 02041 A (W. T. CRANDALL (US)) 23 January 1997 see page 2, line 8-26 see claims 1,5,10,13,14 ---	1,3,4,6, 7
P,X	DATABASE WPI Week 9725 Derwent Publications Ltd., London, GB; AN 97-276677 XP002063288 "Hair treatment agent- comprises extract of Serenoa repens, saw palmetto" see abstract & JP 09 100 220 A (TMC KAREN KK) 15 April 1997 --- -/--	1,4,7,9
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-weight: bold;">27 April 1998</div>		Date of mailing of the international search report  <div style="text-align: center; font-weight: bold;">14/05/1998</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center; font-weight: bold;">Sierra Gonzalez, M</div>

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